Appendix A1: Pending claims (Clean Version of Replacement Claims).

☒ Changes in the pending claims relative to the last version of record are reflected in:

Appendix A2: Changes to claims (redline)(Version With Markings to Show Changes Made).

Please enter any new claims or changes reflected in Appendices A1 and A2.

REMARKS

The status of the claims is as follows:

Amended:	1, 3, 4, 7, 9 and 10
Cancelled:	2, 6, 8 and 11
Pending:	1, 3, 4, 5, 7, 9, and 10

The claim fee status is as follows:

☐ Large Entity
☒ Small Entity

		After Amdmt	Paid for	Fee due for	Fee code
	Independent Claims:	1	3		Lg =102 Sm =202
	Total Claims	7	20	0	Lg =103 Sm =203

The number of total claims and of independent claims remains less than the amount for which fees were previously paid.

The claims have been amended to more clearly define the invention with respect to the election requirement. Support for the amendments is either apparent, or is as described in the text below. Support for the recitation of reducing or ameliorating reduced vascular compliance, elevated pulse pressure and hypertension can be found, for example, at page 19, lines 28-31. No new matter is added.

Conclusion

In light of the above discussion , it is respectfully submitted that the claims are in condition for allowance. The issuance of a Notice of Allowance is earnestly solicited.[2]

Respectfully submitted,

Date: November 12, 2002

Arthur E. Jackson
Registration No. 34,354

Dechert
Princeton Pike Corporate Center
PO Box 5218
Princeton, New Jersey 08543-5218
Allen Bloom (609) 620-3214
Arthur E. Jackson (609) 620-3254
Fax: (609) 620-3259
Attention: Arthur E. Jackson
140952.4.07

---

[2] **FEE DEFICIENCY**

IF ANY ADDITIONAL EXTENSION IS REQUIRED, PLEASE CONSIDER THIS PAPER A PETITION FOR SUCH AN EXTENSION; ANY FEE FOR THE EXTENSION REQUIRED FOR CONSIDERATION OF THIS PAPER BUT NOT ENUMERATED ABOVE OR IN A TRANSMITTAL OR OTHER ASSOCIATED PAPER CAN BE CHARGED TO ACCOUNT NO. 04-0480.

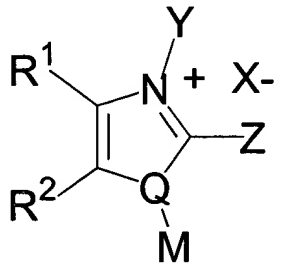
AND/OR

IF ANY ADDITIONAL FEE IS REQUIRED FOR CONSIDERATION OF THIS PAPER, PLEASE CHARGE ACCOUNT NO. 04-0480.

Appendix A1: Pending Claims (Clean Copy)

A1

1. **(Amended)** A method of reducing or ameliorating reduced vascular compliance, elevated pulse pressure and hypertension in an animal, including a human, comprising administering an effective amount of **(A)** a compound of the formula I:



(I)

wherein

a. R^1 and R^2 are

1. independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C_1-C_3)alkylenedioxy, allyl, amino, ω-alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl, alkylsulfinyl, alkylthio, trifluoromethyl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, 4-[C_6 or C_{10}]arylpiperidin-1-yl, 4-[C_6 or C_{10}]arylpiperazin-1-yl, Ar {wherein, consistent with the rules of aromaticity, Ar is C_6 or C_{10} aryl or a 5- or 6-membered heteroaryl ring, wherein 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring can be fused to a benzene, pyridine, pyrimidine, pyridazine, pyrazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Ar)}, Ar–alkyl, Ar-O, $ArSO_2$-, ArSO-, ArS-, $ArSO_2NH$-, ArNH, (N-Ar)(N-alkyl)N-, ArC(O)-, ArC(O)NH-, ArNH-C(O)-, and (N-Ar)(N-alkyl)N-C(O)-, or together R_1 and R_2 comprise methylenedioxy; or

Appendix A: Pending Claims (Clean Copy)-(continued)

2. together with their ring carbons form a C_6- or C_{10}- aromatic fused ring system; or

3. together with their ring carbons form a C_5-C_7 fused cycloalkyl ring having up to two double bonds including the fused double bond of the –olium or –onium containing ring, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo substituents; or

4. together with their ring carbons form a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring may be optionally substituted with one or more 1-pyrrolidinyl-, 4-[C_6 or C_{10}]arylpiperazin-1-yl, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C_1-C_3)alkylenedioxy groups; or

A1 cont.

5. together with their ring carbons form a five to eight membered heterocycle, wherein the heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, and $S(O)_n$, where n=0,1, or 2;

b. Z is

1. hydrogen, alkyl, Ar—CH_2;

2. a group of the formula -$CH(OR^{11})R^{12}$, wherein R^{11} is hydrogen, methyl, ethyl or $CH_3C(O)$-; and R^{12} is [C_1 to C_6]alkyl, Ar, or CO_2R^{13} wherein R^{13} is hydrogen methyl or ethyl;

3. a group of the formula -CH_2WAr, wherein W is -(C=O)- or -$S(O)_n$- where n=1 or 2; or

4. a group of the formula -$CH_2C{\equiv}C$-R^{14}, wherein R^{14} is (C_1-C_6)alkyl;

c. Y is a group of the formula -$CH(R^5)$-R^6 wherein

(a) R^5 is hydrogen, alkyl-, cycloalkyl-, alkenyl-, alkynyl-, aminoalkyl-, dialkylaminoalkyl-, (N-[C_6 or C_{10}]aryl)(N-alkyl)aminoalkyl-, piperidin-1-ylalkyl-, 1-pyrrolidinylalkyl, azetidinylalkyl, 4-alkylpiperazin-1-ylalkyl, 4-alkylpiperidin-1-ylalkyl, 4-[C_6 or C_{10}]arylpiperazin-1-ylalkyl, 4-[C_6 or C_{10}]arylpiperidin-1-ylalkyl, azetidin-1-ylalkyl, morpholin-4-ylalkyl, thiomorpholin-4-ylalkyl, piperidin-1-ylalkyl, [C_6 or C_{10}]aryl, or independently the same as R^6;

(b) R^6 is

Appendix A: Pending Claims (Clean Copy)-(continued)

(1) hydrogen, alkyl (which can be substituted by alkoxycarbonyl), alkenyl, alkynyl, cyano- or Rs, wherein Rs is a C_6 or C_{10} aryl or a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

(2) a group of the formula $-W-R^7$, wherein R^7 is alkyl, alkoxy, hydroxy or Rs, wherein W is -C(=O)- or $-S(O)_n-$ where n=1 or 2;

(3) a group of the formula $-W-OR^8$ wherein R^8 is hydrogen or alkyl,

(4) a group of the formula -CH(OH)Rs; or

(5) a group of the formula $-W-N(R^9)R^{10}$, wherein

A1 cont-

[a] R^9 is hydrogen and R^{10} is an alkyl or cycloalkyl, optionally substituted by

(i) [C_6 or C_{10}]aryl, or

(ii) a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, said heteroaryl ring can be optionally substituted with one or more 1-pyrrolidinyl, 4-[C_6 or C_{10}]arylpiperazin-1-yl, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, and morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C_1-C_3)alkylenedioxy groups, or fused to a substituted phenyl or pyridine ring, wherein the ring fusion is at a carbon-carbon double bond of the heteroaryl ring, or

(iii) a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

[b] R^9 is hydrogen or lower alkyl and R^{10} is Ar; or

[c] R^9 is hydrogen or lower alkyl, and R^{10} is a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms are selected from the group consisting of oxygen, nitrogen and sulfur, said heterocycle; or

[d] R^9 and R^{10} are both alkyl groups; or

[e] R^9 and R^{10} together with N form a heterocycle containing 4-10 ring atoms which can incorporate up to one additional heteroatom selected from the

Appendix A: Pending Claims (Clean Copy)-(continued)

group of N, O or S in the ring, wherein the heterocycle is optionally substituted with (C_6-or C_{10})aryl, (C_6-or C_{10})arylalkyl, or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each such heteroaryl can be optionally substituted with one or more 1-pyrrolidinyl, 4-[C_6 or C_{10}]arylpiperazin-1-yl, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C_1-C_3)alkylenedioxy; or

A1 cont.

[f] R^9 and R^{10} are both hydrogen; or

d. Q is N or S;

e. M is absent when Q is S;

f. M is alkyl, vinyl or allyl, or independently the same as Y; and

g. X is a pharmaceutically acceptable anion, or

(B) a pharmaceutically acceptable salt of the compound,

wherein aryl or Ar can be substituted with, in addition to any substitutions specifically noted, one or more substituents selected from the group consisting of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C_1-C_3)alkylenedioxy, alkylsulfonyl, alkylsulfinyl, ω-alkylenesulfonic acid, alkylthio, allyl, amino, ArC(O)-, ArC(O)NH-, ArO-, Ar-, Ar-alkyl-, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, trifluoromethyl, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, 1-pyrrolidinyl, 4-[C_6 or C_{10}]arylpiperazin-1-yl-, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl; and

wherein heterocycles, except those of Ar, can be substituted with, in addition to any substitutions specifically noted, acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, alkylsulfonyl, alkylsulfinyl, alkylthio, amino, ArC(O)-, ArO-, Ar-, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, sulfamoyl, or trifluoromethyl.

Appendix A: Pending Claims (Clean Copy)-(continued)

A2

3. **(Amended)** The method of claim 1, comprising administering an effective amount of a compound of formula I, wherein Y is according to formula -CH(R^5)-W-R^7.

4. **(Amended)** The method of claim 1, comprising administering an effective amount of a compound of formula I, wherein Y is according to formula -CH(R^5)-W-Rs.

5. The method of Claim 1, comprising administering an effective amount of a compound of formula I, wherein R^1 and R^2 together with their ring carbons form a C_6- or C_{10}- aromatic fused ring which can be substituted by one or more halo, amino, alkyl, sulfonic acid, alkylsulfonyl or ω-alkylenesulfonic acid groups, or a C_1-C_3 alkylenedioxy group with the proviso that when Q is nitrogen R^1 and R^2 do not form a C_6 fused aromatic ring.

7. **(Amended)** The method of Claim 1, comprising administering an effective amount of a compound of formula I, wherein

a. R^1 and R^2 are

A3

1. independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, (C_1-C_3)alkylenedioxy, allyl, ω-alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl, cycloalkyl, halo, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl, alkylsulfinyl, alkylthio, trifluoromethyl, Ar {wherein, consistent with the rules of aromaticity, Ar is C_6 or C_{10} aryl or a 5- or 6-membered heteroaryl ring, wherein 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring can be fused to a benzene, pyrimidine, pyridazine, pyrazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Ar)}, Ar–alkyl, Ar-O, ArSO_2-, ArSO-, ArS-, ArSO_2NH-, ArNH, (N-Ar)(N-alkyl)N-, ArC(O)-, ArC(O)NH-, ArNH-C(O)-, and (N-Ar)(N-alkyl)N-C(O)-; or

2. together with their ring carbons form a C_6- or C_{10}- aromatic fused ring system; or

Appendix A: Pending Claims (Clean Copy)-(continued)

3. together with their ring carbons form a C_5-C_7 fused cycloalkyl ring having up to two double bonds including the fused double bond of the –olium or –onium containing ring, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, aminocarbonyl, carboxy, fluoro, or oxo substituents; or
4. together with their ring carbons form a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring may be optionally substituted with one or more halo or (C_1-C_3)alkylenedioxy groups; or
5. together with their ring carbons form a five to eight membered heterocycle, wherein the heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, and $S(O)_n$, where n=0, 1, or 2;

A3 cont.

b. Z is

1. hydrogen, alkyl, Ar—CH_2;
2. a group of the formula -$CH(OR^{11})R^{12}$, wherein R^{11} is hydrogen, methyl, ethyl or $CH_3C(O)$- ; and R^{12} is [C_1 to C_6]alkyl, Ar, or CO_2R^{13} wherein R^{13} is hydrogen methyl or ethyl;
3. a group of the formula -CH_2WAr, wherein W is -(C=O)- or -$S(O)_n$- where n=1 or 2; or
4. a group of the formula -$CH_2C{\equiv}C$-R^{14}, wherein R^{14} is (C_1-C_6)alkyl;

c. Y is a group of the formula -$CH(R^5)$-R^6 wherein

(a) R^5 is hydrogen or alkyl;

(b) R^6 is

(1) hydrogen, alkyl (which can be substituted by alkoxycarbonyl), alkenyl, alkynyl, cyano- or Rs, wherein Rs is a C_6 or C_{10} aryl or a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

(2) a group of the formula –W–R^7, wherein R^7 is alkyl, alkoxy, hydroxy or Rs, wherein W is -C(=O)- or –$S(O)_n$– where n=1 or 2;

(3) a group of the formula –W–OR^8 wherein R^8 is hydrogen or alkyl,

(4) a group of the formula -CH(OH)Rs; or

Appendix A: Pending Claims (Clean Copy)-(continued)

(5) a group of the formula $-W-N(R^9)R^{10}$, wherein

[a] R^9 is hydrogen and R^{10} is an alkyl or cycloalkyl, optionally substituted by

(i) [C_6 or C_{10}]aryl, or

(ii) a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, said heteroaryl ring can be optionally substituted with one or more halo or (C_1-C_3)alkylenedioxy groups, or fused to a substituted phenyl, or

(iii) a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

A3 cont.

[b] R^9 is hydrogen or lower alkyl and R^{10} is Ar; or

[c] R^9 is hydrogen or lower alkyl, and R^{10} is a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms are selected from the group consisting of oxygen, nitrogen and sulfur, said heterocycle; or

[d] R^9 and R^{10} are both alkyl groups; or

[e] R^9 and R^{10} together with N form a heterocycle containing 4-10 ring atoms which can incorporate up to one additional heteroatom selected from the group of N, O or S in the ring, wherein the heterocycle is optionally substituted with (C_6-or C_{10})aryl, (C_6-or C_{10})arylalkyl, or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each such heteroaryl can be optionally substituted with one or more halo or (C_1-C_3)alkylenedioxy; or

[f] R^9 and R^{10} are both hydrogen; or

d. Q is N or S;

e. M is absent when Q is S;

f. M is alkyl, vinyl or allyl, or independently the same as Y; and

Appendix A: Pending Claims (Clean Copy)-(continued)

g. X is a pharmaceutically acceptable anion, or

(B) a pharmaceutically acceptable salt of the compound,

wherein aryl or Ar can be substituted with, in addition to any substitutions specifically noted, one or more substituents selected from the group consisting of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, $(C_1\text{-}C_3)$alkylenedioxy, alkylsulfonyl, alkylsulfinyl, ω-alkylenesulfonic acid, alkylthio, allyl, ArC(O)-, ArC(O)NH-, ArO-, Ar-, Ar-alkyl-, carboxy, carboxyalkyl, cycloalkyl, halo, trifluoromethyl, hydroxy, $(C_2\text{-}C_6)$hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid; and

A3 cont.

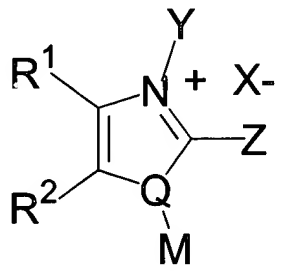
wherein heterocycles, except those of Ar, can be substituted with, in addition to any substitutions specifically noted, acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylsulfonyl, alkylsulfinyl, alkylthio, ArC(O)-, ArO-, Ar-, carboxy, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, sulfamoyl, or trifluoromethyl.

A4 9. **(Amended)** The method of claim 7, comprising administering an effective amount of a compound of formula I, wherein Y is according to formula $-CH(R^5)\text{-}W\text{-}R^7$.

10. **(Amended)** The method of claim 7, comprising administering an effective amount of a compound of formula I, wherein Y is according to formula $-CH(R^5)\text{-}W\text{-}Rs$.

Appendix A2: Version With Markings To Show Changes Made

1. **(Amended)** A method of treating or ameliorating an indication of the invention in an animal, including a human, comprising administering an effective amount of **(A)** a compound of the formula I:



(I)

wherein

a. R^1 and R^2 are

1. independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C_1-C_3)alkylenedioxy, allyl, amino, ω-alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl, alkylsulfinyl, alkylthio, trifluoromethyl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, 4-[C_6 or C_{10}]arylpiperidin-1-yl, 4-[C_6 or C_{10}]arylpiperazin-1-yl, Ar **{**wherein, consistent with the rules of aromaticity, Ar is C_6 or C_{10} aryl or a 5- or 6-membered heteroaryl ring, wherein 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring can be fused to a benzene, pyridine, pyrimidine, pyridazine, pyrazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Ar)**}**, Ar–alkyl, Ar-O, $ArSO_2$-, ArSO-, ArS-, $ArSO_2NH$-, ArNH, (N-Ar)(N-alkyl)N-, ArC(O)-, ArC(O)NH-, ArNH-C(O)-, and (N-Ar)(N-alkyl)N-C(O)-, or together R_1 and R_2 comprise methylenedioxy; or

Appendix A2: Version With Markings To Show Changes Made - (continued)

2. together with their ring carbons form a C_6- or C_{10}- aromatic fused ring system; or

3. together with their ring carbons form a C_5-C_7 fused cycloalkyl ring having up to two double bonds including the fused double bond of the –olium or –onium containing ring, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo substituents; or

4. together with their ring carbons form a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring may be optionally substituted with one or more 1-pyrrolidinyl-, 4-[C_6 or C_{10}]arylpiperazin-1-yl, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C_1-C_3)alkylenedioxy groups; or

5. together with their ring carbons form a five to eight membered heterocycle, wherein the heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, and $S(O)_n$, where n=0,1, or 2;

b. Z is

1. hydrogen, alkyl, Ar—CH_2;

~~**2. a group of the formula $-NR^3R^4$, wherein R^3 and R^4 may be independently hydrogen, alkyl, Ar, or Ar—alkyl ;**~~

2. ~~**3.**~~ a group of the formula $-CH(OR^{11})R^{12}$, wherein R^{11} is hydrogen, methyl, ethyl or $CH_3C(O)$-; and R^{12} is [C_1 to C_6]alkyl, Ar, or CO_2R^{13} wherein R^{13} is hydrogen methyl or ethyl;

~~**4. a group of the formula $-C(CO_2R^{13})(OR^{11})R^{12}$**~~

3. ~~**5.**~~ a group of the formula $-CH_2WAr$, wherein W is -(C=O)- or $-S(O)_n$- where n=1 or 2; or

4. ~~**6.**~~ a group of the formula $-CH_2C{\equiv}C-R^{14}$, wherein R^{14} is (C_1-C_6)alkyl;

c. Y is

~~**1. amino, or**~~

~~**2.**~~ a group of the formula $-CH(R^5)-R^6$ wherein

Appendix A2: Version With Markings To Show Changes Made - (continued)

(a) R^5 is hydrogen, alkyl-, cycloalkyl-, alkenyl-, alkynyl-, aminoalkyl-, dialkylaminoalkyl-, (N-[C_6 or C_{10}]aryl)(N-alkyl)aminoalkyl-, piperidin-1-ylalkyl-, 1-pyrrolidinylalkyl, azetidinylalkyl, 4-alkylpiperazin-1-ylalkyl, 4-alkylpiperidin-1-ylalkyl, 4-[C_6 or C_{10}]arylpiperazin-1-ylalkyl, 4-[C_6 or C_{10}]arylpiperidin-1-ylalkyl, azetidin-1-ylalkyl, morpholin-4-ylalkyl, thiomorpholin-4-ylalkyl, piperidin-1-ylalkyl, [C_6 or C_{10}]aryl, or independently the same as R^6;

(b) R^6 is

(1) hydrogen, alkyl (which can be substituted by alkoxycarbonyl), alkenyl, alkynyl, cyano- or Rs, wherein Rs is a C_6 or C_{10} aryl or a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

(2) a group of the formula –W–R^7, wherein R^7 is alkyl, alkoxy, hydroxy or Rs, wherein W is -C(=O)- or –$S(O)_n$– where n=1 or 2;

(3) a group of the formula –W–OR^8 wherein R^8 is hydrogen or alkyl,

(4) a group of the formula -CH(OH)Rs; or

(5) a group of the formula –W–$N(R^9)R^{10}$, wherein

[a] R^9 is hydrogen and R^{10} is an alkyl or cycloalkyl, optionally substituted by

(i) [C_6 or C_{10}]aryl, or

(ii) a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, said heteroaryl ring can be optionally substituted with one or more 1-pyrrolidinyl, 4-[C_6 or C_{10}]arylpiperazin-1-yl, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, and morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C_1-C_3)alkylenedioxy groups, or fused to a substituted phenyl or pyridine ring, wherein the ring fusion is at a carbon-carbon double bond of the heteroaryl ring, or

Appendix A2: Version With Markings To Show Changes Made - (continued)

(iii) a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

[b] R^9 is hydrogen or lower alkyl and R^{10} is Ar; or

[c] R^9 is hydrogen or lower alkyl, and R^{10} is a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms are selected from the group consisting of oxygen, nitrogen and sulfur, said heterocycle; or

[d] R^9 and R^{10} are both alkyl groups; or

[e] R^9 and R^{10} together with N form a heterocycle containing 4-10 ring atoms which can incorporate up to one additional heteroatom selected from the group of N, O or S in the ring, wherein the heterocycle is optionally substituted with (C_6-or C_{10})aryl, (C_6-or C_{10})arylalkyl, or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each such heteroaryl can be optionally substituted with one or more 1-pyrrolidinyl, 4-[C_6 or C_{10}]arylpiperazin-1-yl, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C_1-C_3)alkylenedioxy; or

[f] R^9 and R^{10} are both hydrogen; or

d. Q is N~~,O~~ or S;

e. M is absent when Q is ~~O or~~ S;

f. M is alkyl, vinyl or allyl, or independently the same as Y; and

g. X is a pharmaceutically acceptable anion, or

(B) a pharmaceutically acceptable salt of the compound,

wherein aryl or Ar can be substituted with, in addition to any substitutions specifically noted, one or more substituents selected from the group consisting of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C_1-C_3)alkylenedioxy, alkylsulfonyl, alkylsulfinyl, ω-alkylenesulfonic acid,

Appendix A2: Version With Markings To Show Changes Made - (continued)

alkylthio, allyl, amino, ArC(O)-, ArC(O)NH-, ArO-, Ar-, Ar-alkyl-, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, trifluoromethyl, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, 1-pyrrolidinyl, 4-[C_6 or C_{10}]arylpiperazin-1-yl-, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl; and

wherein heterocycles, except those of Ar, can be substituted with, in addition to any substitutions specifically noted, acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, alkylsulfonyl, alkylsulfinyl, alkylthio, amino, ArC(O)-, ArO-, Ar-, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, sulfamoyl, or trifluoromethyl.

3. **(Amended)** The method of claim 1 ~~2~~, comprising administering an effective amount of a compound of formula I, wherein Y is according to formula -CH(R^5)-W-R^7.

4. **(Amended)** The method of claim 1 ~~2~~, comprising administering an effective amount of a compound of formula I, wherein Y is according to formula -CH(R^5)-W-Rs.

7. **(Amended)** The method of Claim 1, comprising administering an effective amount of a compound of formula I, wherein

a. R^1 and R^2 are

1. independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, (C_1-C_3)alkylenedioxy, allyl, ω-alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl, cycloalkyl, halo, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl, alkylsulfinyl, alkylthio, trifluoromethyl, Ar {wherein, consistent with the rules of aromaticity, Ar is C_6 or C_{10} aryl or a 5- or 6-membered heteroaryl ring, wherein 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to

Appendix A2: Version With Markings To Show Changes Made - (continued)

two atoms of N, each heteroaryl ring can be fused to a benzene, pyrimidine, pyridazine, pyrazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Ar)}, Ar–alkyl, Ar-O, $ArSO_2$-, ArSO-, ArS-, $ArSO_2NH$-, ArNH, (N-Ar)(N-alkyl)N-, ArC(O)-, ArC(O)NH-, ArNH-C(O)-, and (N-Ar)(N-alkyl)N-C(O)-; or

2. together with their ring carbons form a C_6- or C_{10}- aromatic fused ring system; or

3. together with their ring carbons form a C_5-C_7 fused cycloalkyl ring having up to two double bonds including the fused double bond of the –olium or –onium containing ring, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, aminocarbonyl, carboxy, fluoro, or oxo substituents; or

4. together with their ring carbons form a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring may be optionally substituted with one or more halo or (C_1-C_3)alkylenedioxy groups; or

5. together with their ring carbons form a five to eight membered heterocycle, wherein the heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, and $S(O)_n$, where n=0, 1, or 2;

b. Z is

1. hydrogen, alkyl, Ar—CH_2;

~~2. a group of the formula $-NR^3R^4$, wherein R^3 and R^4 may be independently hydrogen, alkyl, Ar, or Ar—alkyl ;~~

2. ~~3.~~ a group of the formula $-CH(OR^{11})R^{12}$, wherein R^{11} is hydrogen, methyl, ethyl or $CH_3C(O)$-; and R^{12} is [C_1 to C_6]alkyl, Ar, or CO_2R^{13} wherein R^{13} is hydrogen methyl or ethyl;

~~4. a group of the formula $-C(CO_2R^{13})(OR^{11})R^{12}$~~

3. ~~5.~~ a group of the formula $-CH_2WAr$, wherein W is -(C=O)- or $-S(O)_n$- where n=1 or 2; or

4. ~~6.~~ a group of the formula $-CH_2C{\equiv}C-R^{14}$, wherein R^{14} is (C_1-C_6)alkyl;

c. Y is

Appendix A2: Version With Markings To Show Changes Made - (continued)

~~1. amino, or~~

~~2.~~ a group of the formula $-CH(R^5)-R^6$ wherein

(a) R^5 is hydrogen or alkyl;

(b) R^6 is

(1) hydrogen, alkyl (which can be substituted by alkoxycarbonyl), alkenyl, alkynyl, cyano- or Rs, wherein Rs is a C_6 or C_{10} aryl or a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

(2) a group of the formula $-W-R^7$, wherein R^7 is alkyl, alkoxy, hydroxy or Rs, wherein W is -C(=O)- or $-S(O)_n-$ where n=1 or 2;

(3) a group of the formula $-W-OR^8$ wherein R^8 is hydrogen or alkyl,

(4) a group of the formula -CH(OH)Rs; or

(5) a group of the formula $-W-N(R^9)R^{10}$, wherein

[a] R^9 is hydrogen and R^{10} is an alkyl or cycloalkyl, optionally substituted by

(i) [C_6 or C_{10}]aryl, or

(ii) a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, said heteroaryl ring can be optionally substituted with one or more halo or (C_1-C_3)alkylenedioxy groups, or fused to a substituted phenyl, or

(iii) a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

[b] R^9 is hydrogen or lower alkyl and R^{10} is Ar; or

[c] R^9 is hydrogen or lower alkyl, and R^{10} is a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms are selected from the group consisting of oxygen, nitrogen and sulfur, said heterocycle; or

[d] R^9 and R^{10} are both alkyl groups; or

Appendix A2: Version With Markings To Show Changes Made - (continued)

[e] R^9 and R^{10} together with N form a heterocycle containing 4-10 ring atoms which can incorporate up to one additional heteroatom selected from the group of N, O or S in the ring, wherein the heterocycle is optionally substituted with (C_6-or C_{10})aryl, (C_6-or C_{10})arylalkyl, or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each such heteroaryl can be optionally substituted with one or more halo or (C_1-C_3)alkylenedioxy; or

[f] R^9 and R^{10} are both hydrogen; or

d. Q is N~~, O~~ or S;

e. M is absent when Q is ~~O or~~ S;

f. M is alkyl, vinyl or allyl, or independently the same as Y; and

g. X is a pharmaceutically acceptable anion, or

(B) a pharmaceutically acceptable salt of the compound,

wherein aryl or Ar can be substituted with, in addition to any substitutions specifically noted, one or more substituents selected from the group consisting of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, (C_1-C_3)alkylenedioxy, alkylsulfonyl, alkylsulfinyl, ω-alkylenesulfonic acid, alkylthio, allyl, ArC(O)-, ArC(O)NH-, ArO-, Ar-, Ar-alkyl-, carboxy, carboxyalkyl, cycloalkyl, halo, trifluoromethyl, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid; and

wherein heterocycles, except those of Ar, can be substituted with, in addition to any substitutions specifically noted, acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylsulfonyl, alkylsulfinyl, alkylthio, ArC(O)-, ArO-, Ar-, carboxy, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, sulfamoyl, or trifluoromethyl.

Appendix A2: Version With Markings To Show Changes Made - (continued)

9. **(Amended)** The method of claim 7 ~~8~~, comprising administering an effective amount of a compound of formula I, wherein Y is according to formula $-CH(R^5)-W-R^7$.

10. **(Amended)** The method of claim 7 ~~8~~, comprising administering an effective amount of a compound of formula I, wherein Y is according to formula $-CH(R^5)-W-Rs$.